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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,104	01/16/2001	Anne N. Murphy	660088.438	8241

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EXAMINER
SIEW, JEFFREY

ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 10/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/765,104	Applicant(s) MURPHY ET AL.	
	Examiner Jeffrey Siew	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,43-59 and 64-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,43-59 and 64-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The amendment filed 7/9/02 has been entered and an office action follows. Claims 1-21,43-59 & 64-96 are pending.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

3. The labeling in the Graph of Figure 7-13 A is difficult to read. Correction is required.

The response states that corrected drawings were submitted in the 7/9/02 filing. No corrected drawings were located at this time. The following is provided to aid the response in filing drawing changes.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY THE AMENDMENT

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21,43-59 & 64-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-21,43-59 & 64-96 are indefinite because it is unclear as to what conditions or steps are involved that would permit identification of mitochondrial calcium uniporter activity and mitochondrial uncoupler or respiratory inhibitor activity. While the specification may describe adding an agent that effects the unicoupler activity or measuring the

uniporter activity or the use of specific dyes, the limitation of the specification are not read into the claims. It is unclear as to what scope the term "conditions" would encompass e.g ion concentrations, candidate agent concentrations or whether conditions refers to the active steps of measuring such activity.

B) Claims 1-21,43-59 & 64-96 are confusing because they are drawn to a method but no clear and defined steps are recited. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion and clearly refer back to the preamble of the claim. See ex parte Erlich, 3 USPQ2, p. 1011 (Bd. Pat. A.P. In. 1986). It is unclear as to whether uniporter activity and mitochondrial uncoupler or respiratory inhibitor activity is measured or not. The claims should be amended to set forth active steps of identification of mitochondrial calcium uniporter activity and mitochondrial uncoupler or respiratory inhibitor activity

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1,3,4,6-14,16-22, 93 & 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Litsky et al (Biochemistry vol. 26 pp. 7071-7080 1997) in further view of Murphy et al (PNAS vol 93 pp. 9893-9898 1996) and Marban et al (US6,183,948 Feb. 6, 2001).

Matlib et al teach the assay of the effect of ruthenium amine complex and Ru360 on Ca++ uptake in mitochondria in vitro and in situ in single cardiac myocytes (see whole doc. esp. abstract). They teach that Ruthenium Red and Ru360, a known inhibitor of Ca++ uniporter which are expressed in cells inhibited uptake. They prepared mitochondria by isolated by centrifugation. They also prepared the cells with digitonin permeabilization and placed cells on a stage in inverted microscope(see page 10224). In Figure 2 they measure different concentrations of ruthenium red in zero concentration and increasingly greater concentration. The increased concentration of either Ru360 or Ruthenium Red led to greater inhibition of uptake. They also performed time studies over time showing the effect of Ru350 on myocytes and mitochonidria (see figure 8 & 9). They measure calcium uptake by spectrophotometrically using arsenazo III (see page 10224).

Matlib et al do not teach high throughput assay or conditions to detect mitochondrial uniporter activity or mitochondrial uncoupler or respiratory activity or calcium indicator molecule.

Litsky et al teach the assaying mitochondrial Ca2+ uniporter activity by the addition of EGTA plus free Mg2+ over time (see abstract & figure 1). . They teach conditions of adding EGTA which inhibits uniporter activity and is reversed by spermine. Inhibition is restored by external adenine nucleotides in concentration dependant manner. They also teach conditions to

uncouple respiratory and phosphorylation activity by the addition of CCP (see page 7073 Exp. Proc. Left top column). They also teach the isolation of mitochondria (see page 7072 Exp. Proc.).

Murphy et al teach calcium green-5N indicator molecules (see page 9894) and they teach expression Bcl2 in mitochondrial membranes of neuronal cells (see abstract)

Marban et al teach of high through put screening for testing a range of chemicals in mitochondrial effects (see col. 8 line 3-10).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Litsky et al's invention to Matlib et al in order to elucidate the interplay between mitochondria and other cell components in cell signaling involving CA++ and role of Ca++ in controlling ATP production (see page 7079). Litsky et al teach that the addition of candidate agents such as EGTA, Adenine and CCP would lead to increased understanding of uniporter models as gated channel that is controlled in part by external effector sites that accept divalent cations or nucleotides. It would have been prima facie obvious to apply Litsky et al's candidate agents to Matlib whole cell studies in order to study the uniporter activity on whole cell level.

Moreover, one of ordinary skill in the art would have been motivated to apply Murphy et al's Calcium green-5N to the combined assay of Litsky et al and Matlib et al in order to accurately detect Ca2+ concentration in real time. Murphy et al state that the fluorescent indicator molecules provides a more suitable measurement in micromolecular concentrations than other dyes and would avoid the costly and procedure intensive radioactive $^{45}CaCl_2$ tracer as used by Matlib. It would have been prima facie obvious to apply Murphy et al's Calcium green-

5N to Litsky et al and Matlibs assay in order to detect micromolar concentrations of Ca++ during the assay.

Moreover, one of ordinary skill in the art would have been motivated to apply Marban et al's teaching of high throughput assays to the combined assay of Matlib et al and Litsky et al in order to screen multiple reagents and different concentrations and their effects of Ca++ uptake. As it was well known and commonly practiced in the art to employ high throughput assays to examine a plurality of samples quickly, it would have been prima facie obvious to apply Marban et al's teaching of high throughput methods to Matlib et al's assay in order to screen many samples for their effect of Ca++ uptake in mitochondria.

7. Claims 2, 5, 43-56,58 & 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Litsky et al (Biochemistry vol. 26 pp. 7071-7080 1997), Murphy et al (PNAS vol 93 pp. 9893-9898 1996) and Marban et al (US6,183,948 Feb. 6, 2001) in further view of McCormack et al (Biochimica et Biophysica Acta vol. 973 no. 420-427 1989 pp. 420-427).

The teachings and suggestions of Matlib et al , Litskey et al, Murphy et al and Marban et al are described previously.

Matlib et al (primary reference) do not teach ionophore such as ionomycin

McCormack et al teach the use of ionomycin which equiblibrates the matrix and extramitochondria (see page 422) and the effects of increasing Ca++ in mitochondria.

One of ordinary skill in the art would have been motivated to add ionomycin to permeabilize the mitochondria in order increase Ca++ stabilization. McCormack et al states that

ionomycin equilibration would allow more accurate Ca++ value calculation. It would have been prima facie obvious to apply McCormick et al's teaching of ionomycin so that an accurate measure of Ca++ concentration would be achieved.

Moreover it would have been prima facie obvious to apply McCormick et al's teaching of repeated contact with increasing Ca++ to Matlib et al's assay in order to examine the effect of increasing extramitochondrial Ca++ concentration.

8. Claims 80-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Litsky et al (Biochemistry vol. 26 pp. 7071-7080 1997) in view of Murphy et al (PNAS vol 93 pp. 9893-9898 1996) in further view of Marban et al (US6,183,948 Feb. 6, 2001).

Litsky et al teach the assaying mitochondrial Ca2+ uniporter activity by the addition of EGTA plus free Mg2+ over time in isolated mitochondria (see abstract & figure 1). They also teach the isolation of mitochondria procedure (see page 7072 Exp. Proc.). They teach conditions of adding EGTA which inhibits uniporter activity and is reversed by spermine. Inhibition is restored by external adenine nucleotides in concentration dependant manner. They also teach conditions to uncouple respiratory and phosphorylation activity by the addition of CCP (see page 7073 Exp. Proc. Left top column).

Litsky et al do not teach high throughput assay or conditions to detect mitochondrial uniporter activity or mitochondrial uncoupler or respiratory activity or calcium indicator molecule.

Murphy et al teach calcium green-5N indicator molecules (see page 9894) and they teach expression Bcl2 in mitochondrial membranes of neuronal cells (see abstract)

Marban et al teach of high through put screening for testing a range of chemicals in mitochondrial effects (see col. 8 line 3-10) and quickly repeating assays steps to reassay agents.

One of ordinary skill in the art would have been motivated to apply Murphy et al's Calcium green-5N to the combined assay of Litsky et al in order to accurately detect Ca2+ concentration in real time. Murphy et al state that the fluorescent indicator molecules provides a more suitable measurement in micromolecular concentrations than other dyes. It would have been prima facie obvious to apply Murphy et al's Calcium green-5N to Litsky et al and Matlibs assay in order to detect micromolar concentrations of Ca++ during the assay.

Moreover, one of ordinary skill in the art would have been motivated to apply Marban et al's teaching of high throughput assays to the combined assay of Litsky et al in order to screen multiple reagents and different concentrations and their effects of Ca++ uptake. As it was well known and commonly practiced in the art to employ high throughput assays to examine a plurality of samples quickly, it would have been prima facie obvious to apply Marban et al's teaching of high throughput methods to Matlib et al's assay in order to screen many samples for their effect of Ca++ uptake in mitochondria.

9. Claims 94 & 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Litsky et al (Biochemistry vol. 26 pp. 7071-7080 1997), Murphy et al (PNAS vol 93 pp. 9893-9898 1996) and Marban et al (US6,183,948 Feb. 6, 2001) in further view of Bernardi et al (JBC vol. 268 1993 pp. 1005-1010).

The teachings and suggestions of Matlib et al, Litsky et al, Murphy et al, Marban et al are described previously.

Matlib et al do not describe cyclosporin.

Bernardi et al teach the effect of cyclosporin on MTP transition pore with Ca ++ ions (see whole document.)

One of ordinary skill in the art would have been motivated to apply Bernardi et al's cyclosporin A to Matlib et al's assay in order to examine the effect of cyclosporin on the Calcium uptake. It would have been prima facie obvious to apply Bernardi et al's cyclosporin A in Matlib et al's assay so that the MTP inhibitory effect on calcium uptake would be examined.

SUMMARY

10. No claims allowed but claims 15, 57,64-79 & 92 are free of the prior art but rejected under 112 second paragraph. Concerning claims 15, 36, 57,75 & 92 here is no prior art that teach or suggest the claimed method further involving transfecting with a gene encoding a calcium uniporter. Concerning claims 64-74 & 76-79 there is no prior art that teach or suggest the claimed method involving permeabilized cell depleted of cytosol.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Siew whose telephone number is (703) 305-3886 and whose e-mail address is Jeffrey.Siew@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can best be reached on weekdays from 6:30 a.m. to 3 p.m. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119.

Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to the Monica Graves for Art Unit 1637 whose telephone number is (703)-306-2938.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-3290 and Before Final FAX (703) 872-9306 or After Final FAX (703) 30872-9307.

JEFFREY SIEW
PRIMARY EXAMINER

October 13, 2002